

Application No. 10/612,497  
Second Supplemental Reply to a March 15, 2005 Office Action  
Second Supplemental Reply Dated June 24, 2005

**Amendments to the Claims:**

Please amend claims 116, 122, 127, 133, 137, 148, 154, 157, 163, 164, 171, 172 and 176 and add claims 231-235. This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1.-115. (Cancelled)

116. (Currently amended) A method for ~~producing~~ expressing and recovering a human monoclonal antibody that competes for binding to CTLA-4 with an antibody comprising the heavy chain CDR amino acid sequences in SEQ ID NO: 1 and the light chain CDR amino acid sequences in SEQ ID NO: 14, wherein said competing human monoclonal antibody inhibits binding of human CTLA-4 to human B7-1 and human B7-2 and wherein said competing human monoclonal antibody comprises a light chain amino acid sequence that utilizes a human A27 V $\kappa$  gene, said method comprising the steps of:

(a) ~~expressing said competing human monoclonal antibody in culturing~~ a mammalian host cell comprising polynucleotides encoding the heavy and light chains of said competing human monoclonal antibody; and

(b) recovering said competing antibody.

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117. (Previously presented) The method according to claim 116, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 or human B7-2 with an  $IC_{50}$  of 100 nM or less.

118. (Previously presented) The method according to claim 116, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 5 nM or less.

119. (Previously presented) The method according to claim 116, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 2 nM or less.

120. (Previously presented) The method according to claim 116, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 5 nM or less.

121. (Previously presented) The method according to claim 116, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 2 nM or less.

122. (Currently amended) The method according to claim 116, wherein a glutamine synthetase expression system is employed for the expression of said competing human monoclonal antibody in said step of expressing said competing antibody.

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123. (Previously presented) The method according to claim 116, wherein said mammalian cell is a CHO cell.

124. (Previously presented) The method according to claim 116, wherein said mammalian cell is an NSO cell.

125. (Cancelled)

126. (Previously presented) The method according to claim 116, wherein said polynucleotides encode the heavy and light chain CDRs of a competing antibody that was generated in a mouse whose genome comprises human immunoglobulin genes.

127. (Currently amended) A method for ~~producing~~ expressing and recovering a human monoclonal antibody that competes for binding to CTLA-4 with an antibody comprising the heavy chain variable region amino acid sequence in SEQ ID NO: 1 and the light chain variable region amino acid sequence in SEQ ID NO: 14, wherein said competing human monoclonal antibody inhibits binding of human CTLA-4 to human B7-1 and human B7-2 and wherein said competing human monoclonal antibody comprises a light chain amino acid sequence that utilizes a human A27 V $\kappa$  gene, said method comprising the steps of:

(a) ~~expressing said competing human monoclonal antibody in~~ culturing a mammalian host cell comprising polynucleotides encoding the heavy and light chains of said competing human monoclonal antibody; and

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(b) recovering said competing antibody.

128. (Previously presented) The method according to claim 127, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 or human B7-2 with an  $IC_{50}$  of 100 nM or less.

129. (Previously presented) The method according to claim 127, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 5 nM or less.

130. (Previously presented) The method according to claim 127, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 2 nM or less.

131. (Previously presented) The method according to claim 127, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 5 nM or less.

132. (Previously presented) The method according to claim 127, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 2 nM or less.

133. (Currently amended) The method according to claim 127, wherein a glutamine synthetase expression system is employed in said step of ~~expressing said competing~~

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antibody culturing a mammalian host cell comprising polynucleotides encoding the heavy and light chains of said competing human monoclonal antibody.

134. (Previously presented) The method according to claim 127, wherein said mammalian cell is a CHO cell.

135. (Previously presented) The method according to claim 127, wherein said mammalian cell is an NSO cell.

136. (Cancelled)

137. (Currently amended) The method according to claim 127, wherein said polynucleotides encode the heavy and light chain CDRs of a competing antibody that was generated in a mouse whose genome comprises human immunoglobulin genes.

138.-147. (Cancelled)

148. (Currently amended) A method for ~~producing~~ expressing and recovering a human monoclonal antibody that specifically binds to CTLA-4, wherein said antibody comprises a light chain that utilizes a human A27 V $\kappa$  gene and inhibits binding of human CTLA-4 to human B7-1 and human B7-2, said method comprising the steps of:

(a) ~~expressing said antibody in~~ culturing a mammalian host cell comprising polynucleotides encoding the heavy and light chains of said antibody[[,]]; and

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(b) recovering said antibody.

149. (Previously presented) The method according to claim 148, wherein said antibody inhibits binding of human CTLA-4 to human B7-1 or human B7-2 with an  $IC_{50}$  of 100 nM or less.

150. (Previously presented) The method according to claim 148, wherein said antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 5 nM or less.

151. (Previously presented) The method according to claim 148, wherein said antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 2 nM or less.

152. (Previously presented) The method according to claim 148, wherein said antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 5 nM or less.

153. (Previously presented) The method according to claim 148, wherein said antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 2 nM or less.

154. (Currently amended) The method according to claim 148, wherein a glutamine synthetase expression system is employed for the expression of said human monoclonal antibody, ~~in said step of expressing said competing antibody~~

155. (Previously presented) The method according to claim 148, wherein said mammalian cell is a CHO cell.

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156. (Previously presented) The method according to claim 148, wherein said mammalian cell is an NSO cell.

157. (Currently amended) A method for ~~producing~~ expressing and recovering a human monoclonal antibody that specifically binds to CTLA-4, wherein said antibody comprises a light chain that utilizes a human A27 V $\kappa$  gene and inhibits binding of human CTLA-4 to human B7-1 and human B7-2, said method comprising the steps of:

- (a) culturing a host cell comprising polynucleotides encoding the heavy and light chains of said antibody; and
- (b) recovering said antibody.

158. (Previously presented) The method according to claim 157, wherein said antibody inhibits binding of human CTLA-4 to human B7-1 or human B7-2 with an IC<sub>50</sub> of 100 nM or less.

159. (Previously presented) The method according to claim 157, wherein said antibody inhibits binding of human CTLA-4 to human B7-1 with an IC<sub>50</sub> of 5 nM or less.

160. (Previously presented) The method according to claim 157, wherein said antibody inhibits binding of human CTLA-4 to human B7-1 with an IC<sub>50</sub> of 2 nM or less.

161. (Previously presented) The method according to claim 157, wherein said antibody inhibits binding of human CTLA-4 to human B7-2 with an IC<sub>50</sub> of 5 nM or less.

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162. (Previously presented) The method according to claim 157, wherein said antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 2 nM or less.

163. (Currently amended) The method according to claim 157, wherein a glutamine synthetase expression system is employed for the expression of said human monoclonal antibody in said step of expressing said competing antibody,

164. (Currently amended) A method for ~~producing~~ expressing and recovering a human monoclonal antibody that competes for binding to CTLA-4 with an antibody comprising the heavy chain variable region amino acid sequence in SEQ ID NO: 1 and the light chain variable region amino acid sequence in SEQ ID NO: 14, wherein said competing human monoclonal antibody inhibits binding of human CTLA-4 to human B7-1 and human B7-2 and wherein said competing human monoclonal antibody comprises a light chain amino acid sequence that utilizes a human A27 V $\kappa$  gene, said method comprising the steps of:

(a) ~~expressing said competing antibody in~~ culturing a host cell comprising polynucleotides encoding the heavy and light chains of said competing human monoclonal antibody[[,]]; and

(b) recovering said competing antibody.



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165. (Previously presented) The method according to claim 164, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 or human B7-2 with an  $IC_{50}$  of 100 nM or less.

166. (Previously presented) The method according to claim 164, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 5 nM or less.

167. (Previously presented) The method according to claim 164, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-1 with an  $IC_{50}$  of 2 nM or less.

168. (Previously presented) The method according to claim 164, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 5 nM or less.

169. (Previously presented) The method according to claim 164, wherein said competing antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 2 nM or less.

170. (Cancelled)

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171. (Currently amended) The method according to claim 164, wherein a glutamine synthetase expression system is employed for the expression of said competing human monoclonal antibody ~~in said step of expressing said competing antibody~~

172. (Currently amended) A method for ~~producing~~ expressing and recovering a human monoclonal antibody that specifically binds to CTLA-4, wherein said antibody possesses a selectivity for human CTLA-4 over human CD28, human B7-2, human CD44, and hIgG1 of greater than 100:1 and inhibits binding between human CTLA-4 and human B7-2 with an  $IC_{50}$  of lower than 5 nM; said method comprising the steps of:

- (a) ~~expressing said antibody in~~ culturing a mammalian host cell comprising polynucleotides encoding the heavy and light chains of said antibody[.]; and
- (b) recovering said antibody.

173. (Previously presented) The method according to claim 172, wherein said antibody inhibits binding of human CTLA-4 to human B7-2 with an  $IC_{50}$  of 2 nM or less.

174. (Previously presented) The method according to claim 172, wherein said light chain amino acid sequence of said antibody utilizes a human A27  $V_k$  gene.

175. (Previously presented) The method according to claim 172, wherein said polynucleotides encode the heavy and light chain CDRs of an antibody that was generated in a mouse whose genome comprises human immunoglobulin genes.

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176. (Currently amended) The method according to claim 172, wherein a glutamine synthetase expression system is employed for the expression of said human monoclonal antibody in said step of expressing said competing antibody.

177. (Previously presented) The method according to claim 176, wherein said mammalian cell is a CHO cell.

178. (Previously presented) The method according to claim 176, wherein said mammalian cell is an NSO cell.

179. (Previously presented) The method according to claim 117, wherein said mammalian cell is a CHO cell.

180. (Previously presented) The method according to claim 117, wherein said mammalian cell is an NSO cell.

181. (Previously presented) The method according to claim 118, wherein said mammalian cell is a CHO cell.

182. (Previously presented) The method according to claim 118, wherein said mammalian cell is an NSO cell.

183. (Previously presented) The method according to claim 119, wherein said mammalian cell is a CHO cell.

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184. (Previously presented) The method according to claim 119, wherein said mammalian cell is an NSO cell.

185. (Previously presented) The method according to claim 120, wherein said mammalian cell is a CHO cell.

186. (Previously presented) The method according to claim 120, wherein said mammalian cell is an NSO cell.

187. (Previously presented) The method according to claim 121, wherein said mammalian cell is a CHO cell.

188. (Previously presented) The method according to claim 121, wherein said mammalian cell is an NSO cell.

189. (Previously presented) The method according to claim 122, wherein said mammalian cell is a CHO cell.

190. (Previously presented) The method according to claim 122, wherein said mammalian cell is an NSO cell.

191. (Cancelled)

192. (Cancelled)

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193. (Previously presented) The method according to claim 126, wherein said mammalian cell is a CHO cell.

194. (Previously presented) The method according to claim 126, wherein said mammalian cell is an NSO cell.

195. (Previously presented) The method according to claim 128, wherein said mammalian cell is a CHO cell.

196. (Previously presented) The method according to claim 128, wherein said mammalian cell is an NSO cell.

197. (Previously presented) The method according to claim 129, wherein said mammalian cell is a CHO cell.

198. (Previously presented) The method according to claim 129, wherein said mammalian cell is an NSO cell.

199. (Previously presented) The method according to claim 130, wherein said mammalian cell is a CHO cell.

200. (Previously presented) The method according to claim 130, wherein said mammalian cell is an NSO cell.

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201. (Previously presented) The method according to claim 131, wherein said mammalian cell is a CHO cell.

202. (Previously presented) The method according to claim 131, wherein said mammalian cell is an NSO cell.

203. (Previously presented) The method according to claim 132, wherein said mammalian cell is a CHO cell.

204. (Previously presented) The method according to claim 132, wherein said mammalian cell is an NSO cell.

205. (Previously presented) The method according to claim 133, wherein said mammalian cell is a CHO cell.

206. (Previously presented) The method according to claim 133, wherein said mammalian cell is an NSO cell.

207. (Cancelled)

208. (Cancelled)

209. (Previously presented) The method according to claim 137, wherein said mammalian cell is a CHO cell.

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210. (Previously presented) The method according to claim 137, wherein said mammalian cell is an NSO cell.

211. (Previously presented) The method according to claim 149, wherein said mammalian cell is a CHO cell.

212. (Previously presented) The method according to claim 149, wherein said mammalian cell is an NSO cell.

213. (Previously presented) The method according to claim 150, wherein said mammalian cell is a CHO cell.

214. (Previously presented) The method according to claim 150, wherein said mammalian cell is an NSO cell.

215. (Previously presented) The method according to claim 151, wherein said mammalian cell is a CHO cell.

216. (Previously presented) The method according to claim 151, wherein said mammalian cell is an NSO cell.

217. (Previously presented) The method according to claim 152, wherein said mammalian cell is a CHO cell.

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218. (Previously presented) The method according to claim 152, wherein said mammalian cell is an NSO cell.

219. (Previously presented) The method according to claim 153, wherein said mammalian cell is a CHO cell.

220. (Previously presented) The method according to claim 153, wherein said mammalian cell is an NSO cell.

221. (Previously presented) The method according to claim 154, wherein said mammalian cell is a CHO cell.

222. (Previously presented) The method according to claim 154, wherein said mammalian cell is an NSO cell.

223. (Cancelled)

224. (Cancelled)

225. (Previously presented) The method according to claim 173, wherein said mammalian cell is a CHO cell.

226. (Previously presented) The method according to claim 173, wherein said mammalian cell is an NSO cell.



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227. (Previously presented) The method according to claim 174, wherein said mammalian cell is a CHO cell.

228. (Previously presented) The method according to claim 174, wherein said mammalian cell is an NSO cell.

229. (Previously presented) The method according to claim 175, wherein said mammalian cell is a CHO cell.

230. (Previously presented) The method according to claim 175, wherein said mammalian cell is an NSO cell.

231. (New) The method according to claim 127, wherein said competing human monoclonal antibody that utilizes a human A27 V $\kappa$  gene comprises the light chain variable region amino acid sequence in SEQ ID NO: 14 and the heavy chain variable region amino acid sequence in SEQ ID NO: 1.

232. (New) The method according to claim 133, wherein said competing human monoclonal antibody that utilizes a human A27 V $\kappa$  gene comprises the light chain variable region amino acid sequence in SEQ ID NO: 14 and the heavy chain variable region amino acid sequence in SEQ ID NO: 1.

233. (New) The method according to claim 134, wherein said competing human monoclonal antibody that utilizes a human A27 V $\kappa$  gene comprises the light chain variable region

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amino acid sequence in SEQ ID NO: 14 and the heavy chain variable region amino acid sequence in SEQ ID NO: 1.

234. (New) The method according to claim 135, wherein said competing human monoclonal antibody that utilizes a human A27 V $\kappa$  gene comprises the light chain variable region amino acid sequence in SEQ ID NO: 14 and the heavy chain variable region amino acid sequence in SEQ ID NO: 1.

235. (New) The method according to claim 157, wherein said human monoclonal antibody that utilizes a human A27 V $\kappa$  gene comprises the light chain variable region amino acid sequence in SEQ ID NO: 14 and the heavy chain variable region amino acid sequence in SEQ ID NO: 1.